Comment

In this case conventional investigations⁴ did not show any aetiological cause for the patient's adverse reaction, but a penicillinase-sensitive penicillin was detected in the donor blood unit.

The patient's history, the symptoms that appeared after the injection of cephazolin, and the results of the rat mast-cell degranulation test leave little doubt about the diagnosis of hypersensitivity to the β -lactam antibiotics. The symptoms appearing after the transfusion of the blood unit containing penicillin were identical with those observed after the injection of cephazolin and consistent with an allergic reaction to penicillin.^{2,3} These findings indicate that the reaction in our patient was related to the presence of penicillin in the transfused blood unit.

Screening of donors at our blood bank includes questioning about the use of drugs. This case shows that this method is not reliable enough and that the presence of penicillins in blood units might induce reactions after transfusion. We suggest that blood units are tested for penicillins, especially when the recipient is known to be allergic to them. Testing is also warranted when conventional methods fail to show any reason for an adverse reaction after transfusion.

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³ Pratt WB. The inhibitors of cell wall synthesis. In: *Fundamentals of chemotherapy*. London: Oxford University Press, 1973:84-118.

⁴ Grumet FC, Yankee RA. Non-cell reactions. In: *New approaches to transfusion reactions*. Washington: American Association of Blood Banks, 1974:39-52.

⁵ Perelmutter L, Khera K. A study on the detection of human reagins with rat peritoneal mast cells. *Int Arch Allergy Appl Immunol* 1970;39:27-44.

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Hadassah University Hospital, Mount Scopus, Jerusalem, Israel

J MICHEL, MD, senior lecturer, department of clinical microbiology

R SHARON, PHD, lecturer in haematology, blood bank

Weight gain between dialyses in diabetics: possible significance of raised intracellular sodium content

Although well-timed renal transplantation, preferably using living related donors, offers the best chance of survival for diabetic patients who develop renal failure¹ regular haemodialysis (RDT) remains a valuable holding therapy. Diabetic patients on RDT face numerous problems,² including difficulty in obtaining reliable access to the circulation and increased prevalence of sepsis related to shunts and fistulae. These patients also gain excessive weight between dialyses² and, because of commonly-associated autonomic neuropathy, the ultrafiltration required with dialysis to correct this may cause undesirable hypotension. We have investigated weight gain between dialyses in a group of eight diabetic patients on RDT over a three-month period and compared them with a matched group of non-diabetic patients treated with RDT over the same period. After discovering grossly abnormal intracellular electrolyte concentrations in one of the diabetic patients we also studied leucocyte intracellular sodium content in a group of diabetic patients on RDT and peritoneal dialysis and compared them with a matched group of non-diabetic uraemic patients also on RDT. Six of the patients from the first part of the study were included in the second part.

Patients, methods, and results

The increase in weight between successive dialyses, separated by two to three days, was recorded over a three-month period. This was then expressed as a percentage of the patient's weight at the end of the previous dialysis and the mean obtained by dividing the total by the number of dialyses. Eight diabetic patients and eight non-diabetics were not significantly different in mean age, number of square metre hours of dialysis per week, urine output, or diuretic therapy. There was, however, a significantly greater

interdialytic weight gain in the diabetic group (4.6% of body weight compared with 2.4%, $p < 0.01$). Intracellular sodium content was measured on peripheral blood leucocytes obtained immediately before dialysis. Leucocytes were separated from about 30 ml venous blood by the method of Baron and Ahmed,³ involving dextran sedimentation of erythrocytes. Trapped extracellular fluid was measured using a ⁵¹Cr EDTA marker. After isolation cells were dried at 100°C to constant weight, treated with 0.1N HNO₃, and electrolyte concentrations determined by flame photometry. Eight diabetic patients who had been on regular dialysis for at least three months, including two patients on peritoneal dialysis, were compared with eight non-diabetics on maintenance haemodialysis. The patients were matched in the same way as in the first group, and in particular there was no significant difference in sodium intake or serum albumin concentration between the two groups. A significantly higher intracellular sodium was found in the diabetic patients (mean $\pm$ SD = 143.4 ± 68.6 mmol/kg dry cell weight v 76.2 ± 30.3 mmol/kg, $p < 0.025$).

Comment

These observations confirm that the interdialytic weight increases in diabetics on dialysis, although this report is the first accurately to quantify this. High intracellular sodium content and concentration accompanied by a raised cell water and low intracellular potassium has been described in uraemia and ascribed to impairment of the ouabain-sensitive sodium pump. These abnormalities return to normal with regular dialysis therapy,⁵ but this has clearly not occurred in the diabetics we have studied since their intracellular sodiums remain high. It has been suggested that hyperglycaemia and possible high concentrations of circulating angiotensin and aldosterone are responsible for increased thirst and weight gain in diabetics on dialysis.² But our results suggest an alternative explanation, since possibly the high white cell sodium content may be mirrored in the central nervous system and acts as a "false signal" to the thirst centres. The failure of regular haemodialysis to reverse this abnormality in diabetics remains unexplained.

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³ Baron DN, Ahmed SA. Intracellular concentration of water and of the principal electrolytes demonstrated by the analysis of isolated human leucocytes. *Clin Sci* 1969;37:205-219.

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Renal and Liver Units, King's College Hospital, London SE5

ROGER JONES, MA, MRCP, research fellow

LUCILLA POSTON, BSC, research biochemist

HUMBERTO HINESTROSA, MD, research fellow

VICTOR PARSONS, DM, FRCP, consultant physician

ROGER WILLIAMS, MD, FRCP, consultant physician

Relapses in primate malaria: discovery of two populations of exoerythrocytic stages. Preliminary note

Shortt and Garnham's¹ discovery in 1948 of exoerythrocytic schizonts of *Plasmodium cynomolgi* in the liver of the rhesus monkey 102 days after the inoculation of sporozoites and just before the onset of a relapse led them to postulate that successive cycles of development in the liver were responsible for the "true" relapse. Further work (see review²) suggested that this idea was invalid, and the alternative theory of dormancy was substituted. In fact, in 1946 Shute³ had already suggested that the sporozoite, or "x body," into which it grew might remain inactive as a resting stage in the host. Apart from the nearly mature exoerythrocytic schizonts which have continued

to be described in late infections of *P. cynomolgi*, *P. vivax*, and *P. ovale*, the actual dormant bodies ("hypnozoites") have remained hypothetical. Krotoski *et al.*⁴ applying the indirect immunofluorescent antibody technique (IFAT), showed that the early stages of *P. cynomolgi* could be recognised in the liver of monkeys as early as 48 hours after infection. Using the same techniques we have found dormant bodies at seven and 50 days.

Methods and results

We inoculated 12 million sporozoites of *P. cynomolgi bastianellii* intravenously into a rhesus monkey and took biopsy specimens of liver tissue at intervals of 2, 12, 24, and 48 hours and 7, 50, and 102 days after infection. The monkey was killed on day 105, when specimens of liver were also taken. The day 7 specimen was taken to confirm that the infection was heavy enough to find easily the early forms of the parasite. Examination of this specimen showed an average of 38 large (mature) schizonts per 4 × 9 mm section, and this was regarded as of sufficient density for our purpose. These bodies were identified in Giemsa-stained material and in sections stained by IFAT; they lay inside parenchymal cells.

To our surprise, the latter sections (of the day 7 biopsy specimen) showed in addition to the normal schizonts of about 35 µm in diameter a population of very small parasites also within the parenchymal cells. These were first identified in the sections subjected to immunofluorescence (figure a). Their

Small form ("hypnozoite") of *P. cynomolgi* in day 7 biopsy specimen of liver, as seen by immunofluorescence (a) and after Giemsa-colophonium staining (b). × 800.

position was recorded (by vernier reading) and the sections were then restained by the Giemsa-colophonium method for confirmation. The identical parasites were then located and showed the following characters: a diameter ranging between 2.9-5.5 µm and averaging 4.5 µm (9 parasites); a single, reddish-purple nucleus surrounded by a clear or variegated bluish cytoplasm; and a fine, yet distinct, limiting membrane (figure b).

The day 50 biopsy specimen was examined by the same techniques and relapse bodies (about 30 µm, as seen previously by various authors) were seen. They were again accompanied by very small forms, similar to those seen in the day 7 biopsy specimen but slightly larger, 5.7-7.0 µm averaging 6.6 µm in diameter (10 parasites), the difference being due to a more abundant cytoplasm; they also possessed a single nucleus. The earliest and the latest biopsy specimens remain to be examined.

Comment

This work may take a year or more to complete. In the meantime we report the present observations, which represent the demonstration at last of the long-sought hypothetical latent stages of the parasite. This work thus lends support to the theory put forward by Shute *et al.*⁵ that certain species of malaria parasites occur in the form of two distinctive populations of sporozoites, one of which undergoes

immediate development in the liver and produces merozoites that invade the blood after a normal prepatent period (7-8 days), and the other in which development is arrested for varying lengthy periods soon after the sporozoite has invaded the parenchymal cell. These are the forms—the "x bodies" or "hypnozoites"—that ultimately become reactivated to complete their development and cause relapses.

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- ² Garnham PCC. The continuing mystery of relapses in malaria. *Protozool Abs* 1977;1:1-12.
- ³ Shute PG. Latency and long-term relapses in benign tertian malaria. *Trans R Soc Trop Med Hyg* 1946;40:189-200.
- ⁴ Krotoski WA, Collins WE, Broderick JR, Warren M, Krotoski DM. The two-day exoerythrocytic form of *Plasmodium cynomolgi*: detection by immunofluorescence. *Proc 4th int Cong Parasit* 1978;C-2:60-1.
- ⁵ Shute PG, Lupascu G, Branzel P, *et al.* A strain of *Plasmodium vivax* characterized by prolonged incubation: the effect of numbers of sporozoites on the length of the prepatent period. *Trans R Soc Trop Med Hyg* 1976;70:474-81.

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Tropical Infectious Disease Research Program, United States Public Health Service Hospital, New Orleans, LA 70118 USA

W A KROTOSKI, MD, PhD, chief of program
D M KROTOSKI, MS, technical assistant

Imperial College of Science and Technology, Department of Zoology and Applied Entomology, Ascot, Berkshire

P C C GARNHAM, CMG, MD, FRS, senior research fellow
R S BRAY, D SC, honorary lecturer (member of Medical Research Council external staff)
R KILLICK-KENDRICK, D SC, honorary lecturer (member of Medical Research Council external staff)

London School of Hygiene and Tropical Medicine, London WC1

C C DRAPER, MA, DM, senior lecturer
G A T TARGETT, PHD, reader in immunology of protozoal infections
M W GUY, FIST, chief medical laboratory scientific officer

ONE HUNDRED YEARS AGO Singular cases occur in medical practice in which the most experienced physicians will find their knowledge and experience fail to furnish the elements of diagnosis. A remarkable example of a case of this kind is related in the *Journal für Öffentliche Gesundheitspflege*, No. 1, 1879, by Dr Landon of Elbing. He had been treating for some years a workman suffering from liver-complaint, which sometimes improved, but from which his patient had never completely recovered. The patient was from time to time attacked with severe bleeding at the nose, which produced great weakness. The bleedings lasted, from time to time, for seven years. At first, they were slight, and then they became more severe, and, later on, generally occurred twice a day. Injection of iced water and other means were employed, which gave temporary relief only. At the same time, the patient complained of a sense of pressure in the upper part of the nostril. Suddenly, one day, after a hard sneezing, there escaped from the left nostril what resembled, on superficial examination, a small round worm, which was full of active movement. It was put into water, and left for a long time. After the expulsion of the worm, the patient improved considerably, the bleeding altogether ceased, and gradually he assumed a healthy aspect. The worm was identified as a young form of the so-called *pentastoma taenioides*. This is an entozoon, which in its states of development inhabits the rectal and nasal apertures of the dog, the wolf, the fox, occasionally the horse, and rarely of man. The early forms live encapsuled in the abdominal and thoracic cavities of the herbivorous animals, especially in the liver, where they give rise to considerable destructive changes. After some time, they escape from the capsule, wander about in the body, and again become encapsuled, and, when the encapsuled creature does not die, new ones are produced. When they are hidden in the flesh of the animal in which they live, they find a home in their host, and lie quiet for a time until they are expelled with the nasal mucus. It is not improbable that, from the frequent taste in Germany for uncooked or imperfectly cooked food, these entozoa enter the human system in the living state; and it would appear in this patient that the previous liver-affection might be due to the entrance into the liver of the *pentastoma* in its embryo state, and that it subsequently passed off as the creature became encapsuled. (*British Medical Journal*, 1880.)